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EXAMINER	
SZNAIDMAN, MARCOS L	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,324	ZELDIS, JEROME B.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *12,13,16-21 and 32-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14,15 and 22-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10 pages / 03/03/06 and 03/31/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on July 23, 2008.

Election/Restrictions

Applicant's election without traverse of Group I (Claims 1-31) and the following species: cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4yl}-amide as the selective cytokine inhibitory drug (from now on compound A), and hydroxyurea as the second active agent in the reply filed on July 23, 2008 is acknowledged.

Status of Claims

Claims 1-40 are currently pending and are the subject of this office action.

Claim 12-13, 16-21, and 32-40 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention/species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 23.

Claims 1-11, 14-15 and 22-31 are presently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5-11, 14-15, and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of managing a

myeloproliferative disease, comprising administering to a patient in need of such management a prophylatically effective amount of a selective cytokine inhibitory drug, does not reasonably provide enablement for a method of preventing and/or treating a myeloproliferative disease comprising administering a therapeutically or prophylactically effective amount of a selective cytokine inhibitory drug The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a scope of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1- the quantity of experimentation necessary,

2- the amount of direction or guidance provided,

3- the presence or absence of working examples,

4- the nature of the invention,

5- the state of the prior art,

6- the relative skill of those in the art,

7- the predictability of the art, and

8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention

Claims 1, 3, 5-11, 14-15, and 22 recite a method of treating or preventing a myeloproliferative disease, which comprises administering an effective amount of a selective cytokine inhibitory drug. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

2. The relative skill of those in the art

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

3. The breadth of the claims

Applicants broadly claim a method of treating or preventing any myeloproliferative disease, comprising administering to a patient in need of such treatment a therapeutically or prophylatically effective amount any cytokine inhibitory drug. The claims further limit the drug to a compound of formula I.

4. The amount of direction or guidance provided and the presence or absence of working examples

The specification teaches that a myeloproliferative disease (MPD) refers to a group of disorders characterized by clonal abnormalities of the hematopoietic stem cells (paragraph 003 of the publication), wherein MPD is further subdivided on the basis of the predominantly proliferating myeloid cell type, e.g., Erythrocyte excess is classified as "polycythemia rubra vera (PRV)" or "polycythemia vera," platelet excess as "primary (or essential) thromobocythemia (PT)," and granulocyte excess as "chronic myelogenous leukemia (CML)." (paragraphs 0004). Moreover, the specification teaches that the precise cause of MPD is not clear and that the treatment of choice for PRV is phlebotomy (paragraph 0015). The specification further teaches that compounds referred to as selective cytokine inhibitory drugs have been synthesized and tested' and have been found to be potent inhibitors of TNF-alpha production. The specification also teaches that these compounds have been found to be potent inhbitors of PDE4, a major phosphodiesterase isozyme found in human myeloid and lymphoid lineage cells. Thus, the specification teaches method of treating or preventing MPD, which comprises administering to a patient in need of such treatment of prevention a therapeutically or

propylatically effective amount of a selective cytokine inhibitory drug (paragraph 0030). With regards to the cytokine inhibitory drug, the specification teaches that cytokine inhibitory drugs include, but are not limited to, cyclic amides such as those of Formula I (paragraph 0049). In addition, the specification provides an in vitro example of modulating, e.g., inhibiting, TNF-alpha production following LPS stimulation. Thus, while the specification provides an in vitro assay of inhibiting TNF-alpha production by a compound encompassed by formula I, the specification appears to be silent on a correlation between the inhibition of TNF-alpha and the treatment or prevention of any and/or all myeloproliferative disorders. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment or prevention of myeloproliferative disorder, is required for practice of the claimed invention.

5. The quantity of experimentation necessary

The quantity of experimentation in the areas of treating a myeloproliferative disorder is extremely large given the unpredictability associated with treating a myeloproliferative disorder with a small organic compound in general and as taught in the specification, the fact that the precise cause of MPD is not clear and preventive regimen is currently available for myeloproliferative disorders. .

6. The state and predictability of the art

The state of the art at the time of filing was such that one of skill could recognize that therapies aimed at treating myeloproliferative disorders have been very disappointing. For example, Mesa (International Journal of Hematology 2002; 76: 296-304) teach that although there are various medical therapies that may palliate aspects of myelofibrosis with myeloid metaplasia (MMM), no medical therapy that has had any demonstratable effect on survival in MMM (page 302, 2nd column, last paragraph). For example, Mesa teach TNF alpha is a cytokine implicated both in the pathogenesis of MMM, as well as being pro-fibrogenic and potentially a direct inhibitor of hematopoiesis and cause of MMM associated constitutional symptoms (page 310, Etanercept). Accordingly, Etanercept, which is a TNF-alpha inhibitor, was piloted in MMM, but did not show any changes in intramedullary manifestation of MMM (page 301, Etanercept). Similarly, Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242) teach a method of treating patients with myeloproliferative disorders comprising administering Enbrel, which is a TNF alpha inhibitor. In particular, the reference teaches that while three patients with AMM improved, no patient had an objective response (page 239, 2nd column, Response). Additionally, Mesa teach that no medical therapy to date has really been shown to have a decisive effect on intramedullary manifestation of the disease (page 302, 2nd column, last paragraph). Thus, at the time the invention was made, those of skill in the art recognize that myeloproliferative disease are difficult to treat, and further, that the majority of medical treatment such as TNF-alpha inhibitors are better suited for palliative therapies than actual treatment of the disease.

7. Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-2, 5 and 10 rejected under 35 U.S.C. 102(a) as being anticipated by Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242).

Claims 1 and 2 recite a method for treating, preventing or managing the therapeutic efficacy of a myeloproliferative disease, which comprises administering to a patient in need of such a treatment a therapeutically effective amount a selective cytokine inhibitory drug. Claim 10 further limits claims 1 or 2, wherein the myeloproliferative disease is agnogenic myeloid metaplasia (AMM).

Tsimberidou et. al. teach a method of treating agnogenic myeloid metaplasia (AMM, a myeloproliferative disease) with Etanercept (Enbrel, an inhibitor of the cytokine

Tumor necrosis factor-alpha (TNF-alpha)) (see abstract). In particular, the reference teach that signs of clinical improvement were noted in some patients, particularly in those with AMM (see page 240, lines 3-5) and they give further experimental data that corroborate these results (see third and fourth paragraph on page 240). Tsimberidou et al. also teach that TNF-alpha is involved in the pathophysiology of myeloproliferative disorders (see introduction on page 237, first three lines).

Claim 5, further limits claim 1 or 2, wherein the patient is refractory to a conventional myeloproliferative disease treatment.

Tsimberidou et. al. further teach that the patients being treated had refractory AMM (a myeloproliferative disease) (see page 238, under Patients and methods-study group).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-2, 5, 10-11, 14-15 and 22-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242) In view of Man et. al. (WO 2001/34606).

Claims 1-2 , 10-11, 14-15 and 28 recite a method for treating, managing or increasing the therapeutic efficacy of a myeloproliferative disease, which comprises administering to a patient in need of such a treatment a therapeutically effective amount of compound A (species elected).

Tsimberidou et. al. teach a method of treating agnogenic myeloid metaplasia (AMM, a myeloproliferative disease) with Etanercept (Enbrel, an inhibitor of the cytokine Tumor necrosis factor-alpha (TNF-alpha)) (see abstract). In particular, the reference teach that signs of clinical improvement were noted in some patients, particularly in those with AMM (see page 240, lines 3-5) and they give further experimental data that corroborate these results (see third and fourth paragraph on page 240). Tsimberidou et. al. further teach that the patients being treated had refractory AMM (a myeloproliferative disease).Tsimberidou et al. also teach that TNF-alpha is involved in the pathophysiology of myeloproliferative disorders (see introduction on page 237, first three lines).

Tsimberidou et. al. do not teach the treatment of AMM or any myeloproliferative disease with compound A.

Man et. al. teach a compound which appears to be 100% identical to compound A claimed in the instant application (see abstract, claim 32 and examples 55 (page 65, for the racemic mixture of compound A), 57 (page 67, for the S isomer of compound A), and example 58 (page 67, for the R isomer of compound A). The WO document further teaches that the compounds are useful for the treatment of disease states mediated by TNF-alpha, wherein the undesirable effects of TNF-alpha are inhibited (page 22, lines 1-5).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to substitute Etanercept as taught by Tsimberidou et a. for the TNFalpha inhibitor taught by Man et al.. One would have been motivated to do so because each have been individually taught in the prior art to be effective at treating diseases related to the undesirable effects of TNF alpha. Hence, one of ordinary skill in the art would have a reasonable expectation of success that by substituting Etanercept as taught by Tsimberidou et a. for the TNF-alpha inhibitor taught by Man et al., one would achieve a method of treating a TNF-alpha associated disease such as myeloproliferation.

Claim 5 further limits claims 1-2, wherein the patient is refractory to a conventional myeloproliferative disease treatment.

For claim 5, Tsimberidou et. al. further teach that the patients being treated had refractory AMM (a myeloproliferative disease) (see page 238, under Patients and methods-study group).

Claim 22 further limits claim 1, wherein compound A is administered before, during or after transplanting umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow in the patient.

Tsimberidou et. al. and Man et. al. teach all the limitations of claim 22, except for the time of administration.

However, since stem cell transplantation is a common procedures in patients with myeloproliferative diseases (as taught by Tsimberidou et al., page 240, 1st column, 2nd full paragraph), it's within the capability of the ordinary artisan to determine a specific administration procedure for a particular patient and adjust that procedure based on the observed clinical effectiveness, thus resulting in the practice of claim 22 with a reasonable expectation of success.

Claims 23-27 recite a method of reducing or avoiding an adverse effect associated with the administration of hydroxyurea (a second active agent) in a patient suffering from a myeloproliferative disease, which comprises administering to a patient in need of such a reduction a therapeutically effective amount of compound A (selective cytokine inhibitor).

As discussed for claims 3-4 and 7-9 above, at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to treat AMM combining two compositions (compound A and hydroxyurea) each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (see MPEP 2144.06). *In re Kerkhoven*,

626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). All this would result in the practice of claims 23-27 with a reasonable expectation of success.

"Avoiding an adverse effect associated with the administration of hydroxyurea by administering compound A" is considered an inherent property of the method taught by Tsimberidou et. al. and Man et. al. (i.e. it was already present in the prior art, even though the prior art does not recognize that property). Although Tsimberidou et. al. and Man et. al. are silent as to "avoiding an adverse effect associated with the administration of hydroxyurea with compound A", applicant has discovered a new property of compound A. This property would have necessarily been present in the method of Tsimberidou et. al. and Man et. al. since the same compounds (compound A and hydroxyurea) are being used for the same purpose: treatment of AMM and given to the same population. In other words, products of identical or similar composition cannot exert mutually exclusive properties when administered under the same circumstances. MPEP 2112 states: "The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer". The explanation of an effect or mechanism of action obtained when using a compound (e.g. reducing adverse effects associated with the administration of hydroxyurea by administering compound A) cannot confer novelty on a known process (administering compound A and hydroxyurea to individuals with AMM) if the skilled artisan was already aware of the occurrence of the desired therapeutic effect. Though new properties of a compound or their mechanism of action are no doubt important contributions to scientific and pharmaceutical development, the assessment of patentability is based upon the therapeutic applications

and effects of the compounds, not the mechanism or properties by which they exert such a therapeutic effect.

Claims 29-31 further limit claim 28, wherein compound A is administered: prior (claim 29), during (claim 30) and after (claim 31) administration of hydroxyurea.

Tsimberidou et. al. and Man et. al. teach all the limitations of claims 29-31, except for the sequence of administration.

However, it's within the capability of the ordinary artisan to determine the sequence administration for a particular patient and adjust that procedure based on the observed clinical effectiveness, thus resulting in the practice of claims 29-31 with a reasonable expectation of success.

Claim 3-4 and 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242) In view of Man et. al. (WO 2001/34606) as applied to claims 1-2, 5, 10-11, 14-15 and 22-31 above, and further in view of Alter et. al. (Blood (1985) 66:373-379).

Claims 3-4 and 7-9 further limit claims 1 and 2, wherein hydroxyurea is used as the second active agent to treat a myeloproliferative disorder.

Tsimberidou et. al. and view of Man et. al. teach all the limitations of claims 3-4 and 7-9, except for using hydroxyurea for the treatment of AMM (a myeloproliferative disorder). However, Alter et. al. teach that hydroxyurea is an effective treatment for AMM (see abstract).

At the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to treat AMM combining two compositions (compound A and hydroxyurea) each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (see MPEP 2144.06). *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). All this would result in the practice of claims 3-4 and 7-9 with a reasonable expectation of success.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242) In view of Man et. al. (WO 2001/34606) as applied to claims 1-2, 5, 10-11, 14-15 and 22-31 above, and further in view of Canepa et. al. (British Journal of Haematology (2001) 115:313-315).

Claim 6 further limits claim 5, wherein the patient is refractory to a myeloproliferative disease treatment comprising thalidomide.

Tsimberidou et. al. and view of Man et. al. teach all the limitations of claim 6, except when the treatment comprises thalidomide. However, Canepa et. al. teach that thalidomide has been used effectively for the treatment of myeloproliferative diseases (i.e. thalidomide is a conventional treatment of myeloproliferative diseases, see title and abstract).

At the time of the invention, it would have been prima facie obvious for the skilled in the art to treat a patient that is refractory to a myeloproliferative disease treatment

comprising thalidomide, since Tsimberidou in the view of Man teach that patients that are refractory to any myeloproliferative disease treatment can be treated with compound A, thus resulting in the practice of claim 6 with a reasonable expectation of success.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
October 27, 2008

/Brandon J Fetterolf/

Primary Examiner, Art Unit 1642